

GIANT CELL AND TAKAYASU ARTERITIS

Sherry D. Scovell, MD, FACS

Disease Definition

The term *vasculitis* refers to a group of inflammatory disorders that specifically affect blood vessels, and *arteritis* refers to inflammation within the arterial side of the circulation. Typically, there is an initial inflammatory process that eventually results in stenosis, occlusion, or aneurysmal degeneration within the affected vessel. The symptoms that develop depend on the vessel affected and the underlying pathologic changes that occur within that vessel. Arteritis is further characterized based on the size of the affected arteries, including those that affect large-size vessels such as the aorta and its branches and those that affect medium- and small-size vessels. Many diseases cause inflammatory large vessel vasculitis [see Table 1]. However, giant cell arteritis (GCA) and Takayasu arteritis (TA) are the most common large vessel vasculitides.

Vascular surgeons should be aware of the workup and management of these two large vessel vasculitides as they are often involved in the care of these patients. Both GCA and TA often result in occlusive and aneurysmal disease involving the aorta and its major branches [see Figure 1]. However, the management of such patients is often distinctly different from the management of patients who present with occlusive disease as a result of atherosclerosis and aneurysmal degeneration due to nonvasculitic etiologies.

Patients with GCA and TA have a few distinct differences, such as age at onset and ethnic background. However, there are also some striking similarities [see Table 2]. Because of these similarities, there has been some discussion that GCA and TA are not entirely separate diseases but that they exist on a spectrum within the same disease state.¹ The Vasculitis Clinical Research Consortium highlighted the fact that arterial involvement was generally symmetrical, in paired vessels, and contiguous with the aorta in both GCA and TA. This observation further serves to support the above theory that these diseases fall in a continuum along the spectrum of one disease state.²

Table 1 Inflammatory Large Vessel Vasculitides*

Giant cell (temporal) arteritis
Takayasu arteritis
Rheumatoid arthritis
Systemic lupus erythematosus
Spondyloarthropathies
Behçet disease
Cogan syndrome
Relapsing polychondritis
Sarcoidosis
Isolated angiitis of the central nervous system

*Giant cell (temporal) arteritis and Takayasu arteritis are two of the most common.

In both GCA and TA, there is an acute inflammatory phase in which the patient presents with nonspecific constitutional symptoms such as fever, malaise, anorexia, and weight loss. However, this stage may be missed or overlooked in many patients due to the nonspecific nature of these symptoms. Often during this inflammatory stage, acute-phase reactants such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are elevated. The resultant sequelae of the inflammation may result in occlusive or aneurysmal arterial disease, leading to distinctly different clinical presentations after the initial acute phase of disease. Medical management is the primary therapy for both GCA and TA. However, surgical or endovascular therapy may be necessary in certain circumstances. This topic review explores all of the above aspects of both GCA and TA.

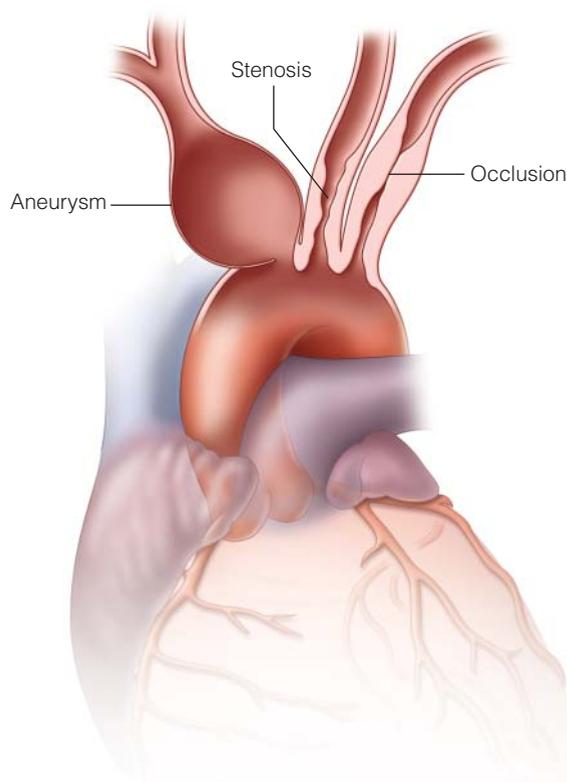
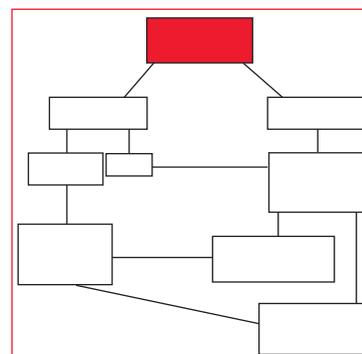


Figure 1 Giant cell arteritis and Takayasu arteritis may result in occlusive disease or aneurysmal disease of the aorta and its branches.

Approach to the Patient with Giant Cell and Takayasu Arteritis

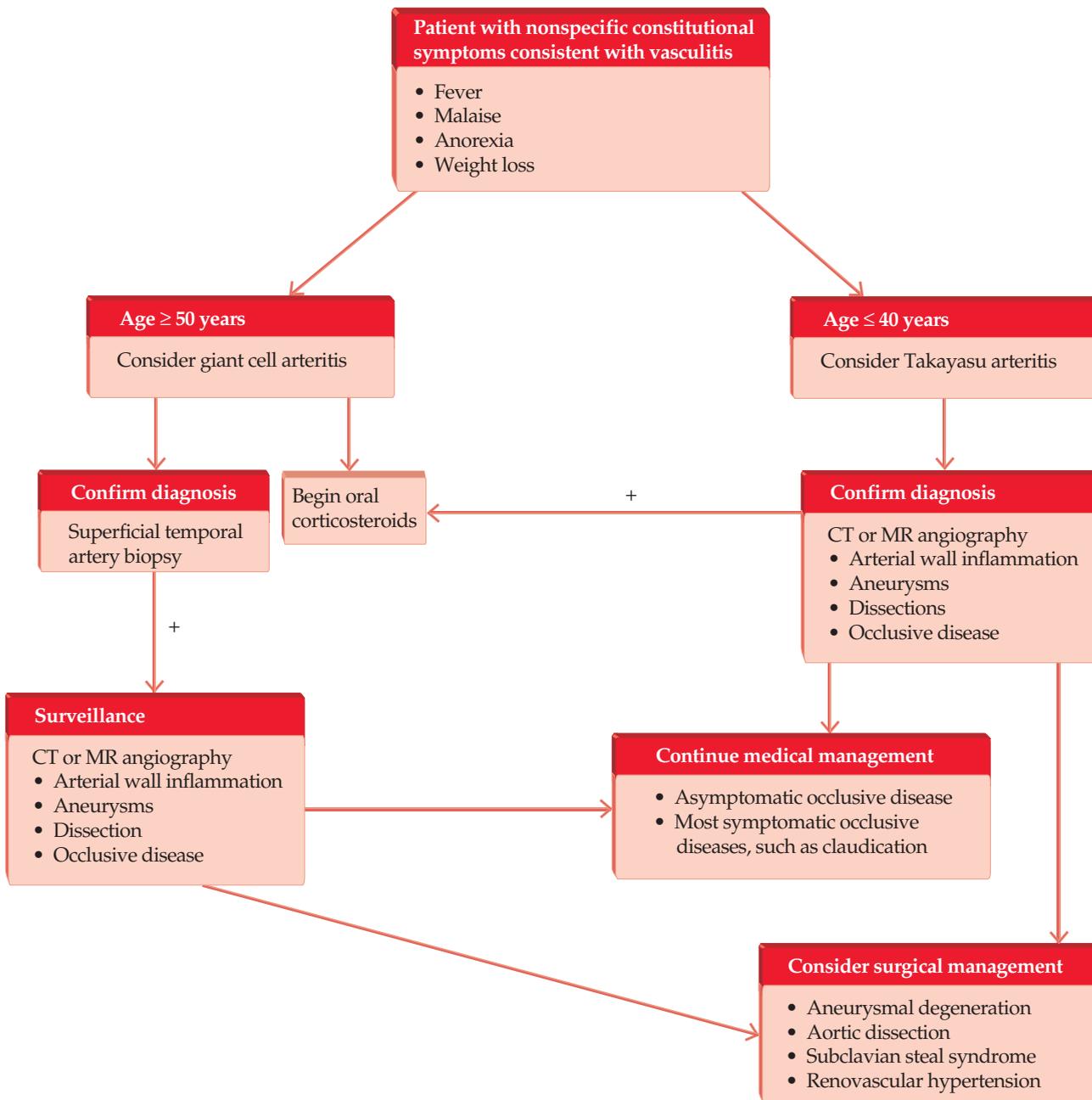


Table 2 Major Differences between Giant Cell Arteritis (GCA) and Takayasu Arteritis (TA)

Factor	GCA	TA
Age at presentation	> 50 years old	< 40 years old
Male-to-female ratio	Slight female predominance	Significant female predominance
Diagnosis	Temporal artery biopsy	Clinical picture with angiographic findings
Medical management	High-dose steroids	High-dose steroids

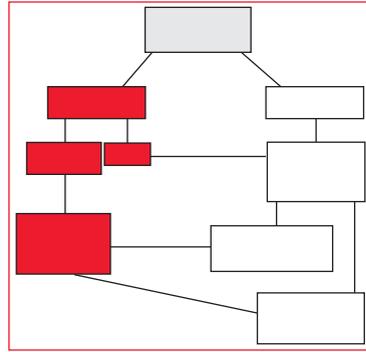
Giant Cell Arteritis/ Temporal Arteritis

GCA, otherwise referred to as temporal arteritis or cranial arteritis, is a primary granulomatous arteritis. In spite of the localizing name of the arteritis, the disease is often widespread in the arterial tree. GCA specifically affects medium- and large-size vessels and especially the branches of the aorta.³ It was first clinically recognized in 1890 when Sir Jonathan Hutchinson described an 80-year-old man with such painful, inflamed temporal arteries that he was unable to comfortably wear his hat.⁴ In 1934, Horton and colleagues described an association between the clinical features and the histopathologic findings, which they termed arteritis temporalis.⁵ The patient with GCA has a wide range of presentations. However, it is critical to appreciate that permanent visual loss can occur in up to 20% of patients if GCA is unrecognized and untreated. Therefore, a high index of suspicion must be maintained to prevent this devastating complication.

EPIDEMIOLOGY

GCA is the most common systemic vasculitis in the Western world.⁶ It is mostly diagnosed in patients over 50 years of age.⁷ Its frequency tends to increase with age, and the peak incidence is in patients around 70 years old.⁸ Overall, there is a slight predominance in women, although a few studies have noted GCA being more common in men.⁹ The highest incidence rates for GCA are in Scandinavian countries, where the annual incidence rate is of around 20 per 100,000 people over the age of 50 years.^{10,11}

There appears to be a clinical connection between GCA and polymyalgia rheumatica, and many experts consider them to be different phases of the same disease. Polymyalgia rheumatica is also an inflammatory disorder with symptoms of aching and morning stiffness in the shoulders, neck, and pelvis. It typically responds to low-dose corticosteroids. Patients with polymyalgia rheumatica are also noted to have an increased incidence in the disease after the age of 50 years, and there is a similar female-to-male ratio as seen in GCA. Population-based studies have shown that approximately 20% of patients with polymyalgia rheumatica have GCA, and, conversely, around 50% of patients with GCA have polymyalgia rheumatica.¹²



ETIOLOGY

The underlying etiology of GCA is unknown, and GCA is considered a primary vasculitis. However, some studies indicate that genetic factors may contribute to the likelihood of developing GCA in some patients through links to genes within the human leukocyte antigen (HLA) region.¹³ Additionally, GCA has also been linked to environmental factors, such as smoking and peripheral vascular disease.¹⁴

DIAGNOSIS

In an attempt to characterize and define the vasculitides, criteria for the diagnosis of GCA were developed. In 1990, a classification system was developed by the American College of Rheumatology. The purpose of this system was to highlight criteria present in GCA to help distinguish it from other vasculitides [see Table 3].¹⁵ For GCA, there are four criteria, including age at onset of disease at or over the age of 50 years, new-onset headache, an increased ESR, and an abnormal superficial temporal artery (STA) biopsy. If three or more criteria are present, there is a sensitivity of 93.5% and a specificity of 91.2% for the diagnosis of GCA.¹⁵

CLINICAL MANIFESTATIONS: HISTORY AND PHYSICAL EXAMINATION

The proper evaluation of any patient begins with a complete history and physical examination. This nonfocused approach is especially important in patients with vasculitides. Many patients initially present with constitutional symptoms that are nonspecific and later have distinctively different symptoms. The symptoms that occur in the later stage of the disease are dependent on the vessels involved in the disease process and the inflammatory and fibrotic changes that occur over time.

Some patients with GCA may present with early systemic, constitutional symptoms such as fever, malaise, anorexia, and weight loss in the inflammatory phase of the disease. In fact, GCA should be considered in any patient with a fever of unknown etiology, especially if in conjunction with an elevated ESR or CRP.

More specific symptoms relatable to GCA are categorized based on whether there is cranial vessel involvement or large vessel involvement. For patients with cranial vessel involvement, two common symptoms include headache and jaw claudication. Two thirds of patients present with headache. The headache is often a new and acute headache centered over the temporal or occipital region and is often refractory to analgesics.¹⁶ Nearly half of patients will complain of jaw claudication. This finding is due to ischemia of the muscles of mastication as a result of intimal proliferation

Table 3 1990 Criteria for the Classification of Giant Cell (Temporal) Arteritis*

Criteria	Explanation
Age at disease onset \geq 50 years old	Development of symptoms or findings beginning at 50 years or older
New headache	New onset of or new type of localized pain in the head
Increased ESR	ESR \geq 50 mm/hr by the Westergren method
Abnormal artery biopsy	Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

ESR = erythrocyte sedimentation rate.

*For the purposes of classification, a patient with vasculitis is said to have giant cell (temporal) arteritis if at least three of these five criteria are present. The presence of any three or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%.¹⁵

and vessel occlusion.¹⁷ Double vision, visual loss, and amaurosis fugax may occur as well. STA tenderness, swelling, or absence of a pulse may be noted.

With respect to large vessel involvement in GCA, patients may present with symptoms related to regions of stenosis or occlusion of aortic branch vessels. These symptoms may develop concurrently with the inflammatory phase or several years after the initial diagnosis.¹⁸⁻²⁰ Clinically, this translates to decreased or absent peripheral pulses on examination or symptoms of upper or lower extremity claudication. It is also important to note that bilateral disease is an extremely common finding.

Because vessel involvement may vary from patient to patient, careful attention must be given to the vascular examination of the patient with suspected arteritis. A head-to-toe examination should be performed. A complete ophthalmologic examination must be conducted. The visual manifestations of GCA may include anterior ischemic optic neuropathy, which translates to a decrease in visual acuity with an afferent pupillary defect. On ophthalmoscopic examination, the optic disk is often swollen. Peripapillary hemorrhages and cotton-wool spots may be noted.²¹ Pallid edema and sectoral edema may be seen with advanced

anterior ischemic optic neuropathy associated with visual loss [see Figure 2 and Figure 3]. Permanent visual loss can occur in up to 20% of patients, especially if GCA is unrecognized and untreated. Unfortunately, this dreaded complication is irreversible but may be prevented with expeditious initiation of corticosteroids.

A complete vascular examination is critical. The STA is one of two terminal branches of the external carotid artery and is easily evaluated due to its superficial position over the temporal bone [see Figure 4]. Beginning with the temporal artery, pulses should be palpated and tenderness over the temporal artery should be evaluated. The carotid artery should be palpated and auscultated for evidence of bruits. An attempt should be made to palpate the subclavian artery pulses in the supraclavicular space as well as all of the upper extremity pulses, such as the axillary, brachial, radial, and ulnar. The infrarenal abdominal aorta should be palpated, as should all lower extremity pulses, including the femoral, popliteal, posterior tibial, and dorsalis pedis. The presence and quality of each pulse should be recorded, as well as any tenderness or evidence of pulse widening indicative of aneurysmal degeneration. Signs of distal embolization from mural thrombus within aneurysms should be noted, as well as any evidence of chronic arterial ischemia.



Figure 2 Pallid edema seen on an ophthalmic examination in the right eye (OD). These findings are consistent with bilateral anterior ischemic optic neuropathy.

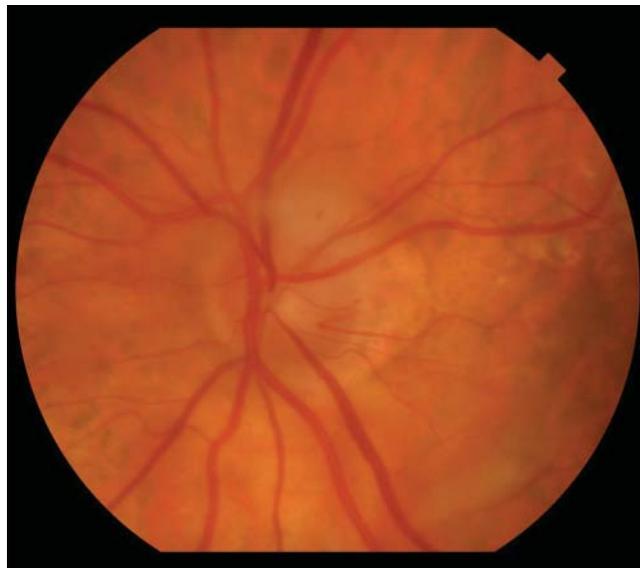


Figure 3 Sectoral edema seen in the left eye (OS). These findings are consistent with bilateral anterior ischemic optic neuropathy.

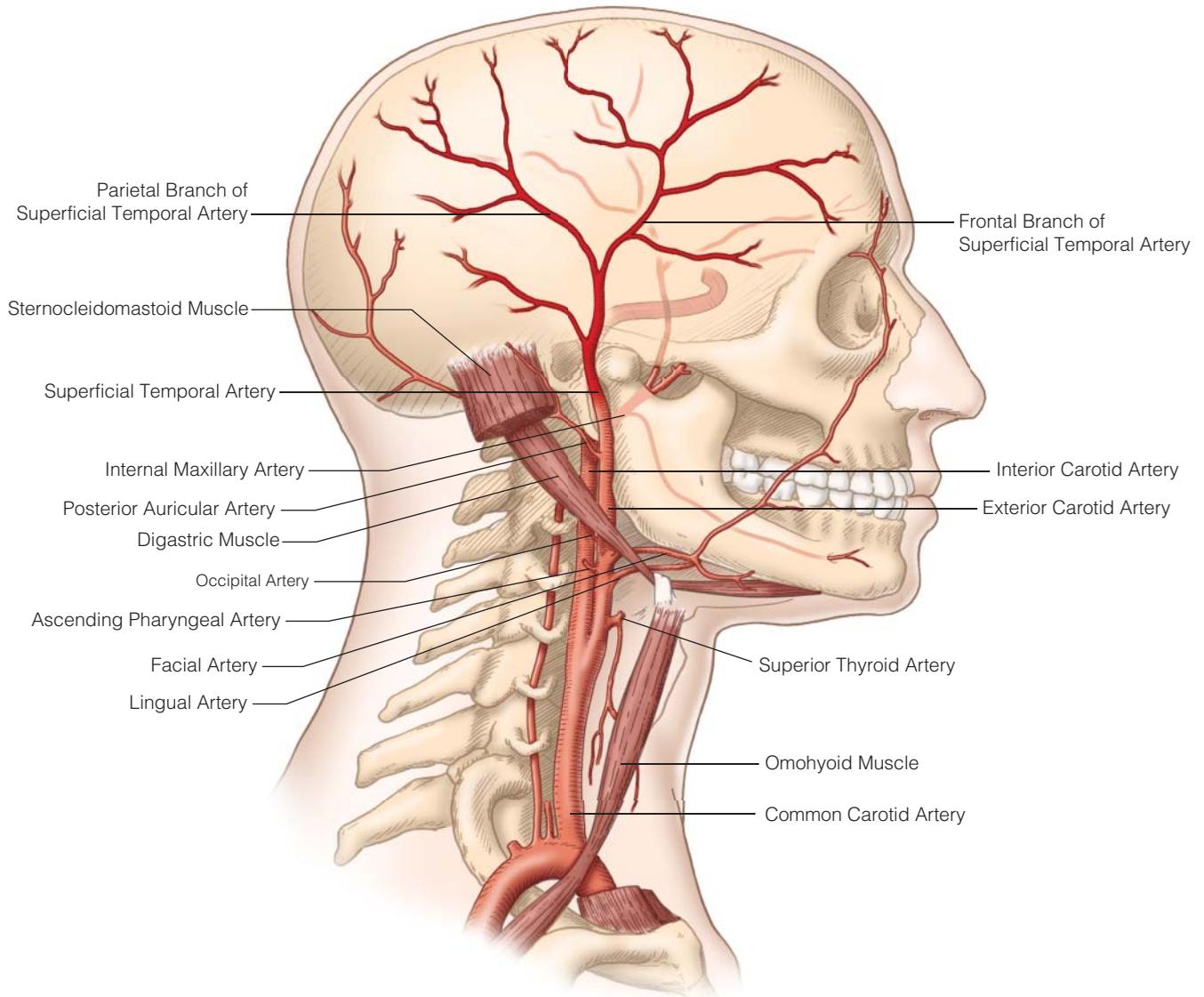


Figure 4 Anatomy of the external carotid artery with its eight branches. The superficial temporal artery is one of two terminal branches.

LABORATORY TESTS

In the initial inflammatory phase, it is customary to check for elevation of acute-phase reactants, such as ESR and CRP. It is important to remember that these acute-phase reactants are neither sensitive nor specific but merely identify the inflammatory nature of these diseases. An ESR of 50 mm/hr or greater is considered one of the classification criteria for GCA. However, it is important to note that up to 10% of patients who are ultimately diagnosed with GCA have an ESR less than 50 mm/hr.²² Therefore, the presence of a normal ESR does not necessarily exclude the diagnosis of GCA.

IMAGING

Other diagnostic tests that may be helpful include ultrasonography, high-resolution magnetic resonance angiography (MRA), or fluorodeoxyglucose positron emission tomography (FDG-PET). These studies may demonstrate inflammatory changes within the arterial wall of the temporal artery.

The presence of a hypoechoic halo around the lumen of the temporal artery on ultrasonography has been demonstrated to have a high specificity for GCA, although its sensitivity is notably lower.²³ Contrast-enhanced MRA may demonstrate bright enhancement of the temporal artery wall, indicative of mural inflammation, which has been found to be highly specific for GCA.²⁴ FDG accumulates in activated inflammatory cells and may be helpful in assessing the activity and extent of the vasculitis in GCA.²⁵ In spite of the above reports, none of these studies provide definitive evidence of GCA and are not routinely used in clinical practice for diagnostic reasons.

CT angiography, conventional angiography, MRA, and ultrasonography are all imaging modalities that are helpful in defining anatomic involvement of large vessels in patients with GCA.^{26,27} The upper extremity arteries are affected more often than the lower extremity arteries. Bilateral, smooth, tapering stenosis or occlusions may be noted in the

subclavian and axillary arteries. Grayson and colleagues documented involvement of the left subclavian artery in 61% of patients and approximately 40% involvement of the axillary arteries.² The thoracic and abdominal aorta were involved 61% and 42% of the time, with carotid and mesenteric involvement less than 20% of the time [see Table 4 and Figure 5].

TISSUE DIAGNOSIS

The definitive diagnosis is not able to be made by imaging modalities. The gold standard in the diagnosis of GCA remains the temporal artery biopsy.^{28,29} Ideally, temporal artery biopsy should be performed prior to the initiation of medical therapy with corticosteroids whenever possible. However, it has been documented that arteritis may still be noted on biopsy within a 2-week period following the initiation of treatment with glucocorticoids. Achkar and colleagues have demonstrated that positivity rates for temporal artery biopsy were similar for those who were untreated and those who received steroid therapy prior to the biopsy (31% versus 35%, respectively).³⁰ In addition, even patients who received doses of more than 15 mg/day of prednisone for longer than a 14-day course in this study exhibited detectable arteritis on histology.

Knowledge of the anatomy of the STA is important. Its origin is behind the mandibular ramus, and it is the terminal branch of the external carotid artery. From the mandibular ramus, the STA then continues superiorly over the posterior aspect of the zygomatic arch. In this region of the zygomatic arch, the facial nerve also crosses the zygoma and travels anteriorly, innervating the frontalis muscle and dividing into temporal and zygomatic branches [see Figure 6]. Just above the zygomatic arch, the STA travels within the superficial temporal or temporoparietal fascia and then divides into frontal and parietal branches. This region of the STA

that is superior to the zygomatic arch and within the superficial temporal fascia is usually far enough away from the facial nerve for safe dissection. The auriculotemporal nerve and the superficial temporal vein travel with the STA, posterior and anterior to the artery, respectively.

STA biopsy is a minor vascular procedure, which is typically performed under local anesthesia in the operating room. There are no contraindications to this outpatient procedure. Most commonly, palpation is used to identify the STA, although duplex ultrasonography may be employed if needed. There may or may not be a palpable pulse over the STA due to the inflammatory changes within the arterial wall. A biopsy of the temporal artery is performed by making an incision over the artery and resecting a portion of it [see Figure 7]. During the procedure, the temporal artery is identified and dissected free from the underlying tissue. All side branches are ligated. The proximal and distal ends of the temporal artery are then ligated, and the skin is closed.

A unilateral biopsy is initially performed as a bilateral temporal artery biopsy does not appear to increase the diagnostic yield.³¹ A recent retrospective study demonstrated that biopsy length does not seem to affect the results.³² Ideally, the length of the temporal artery resected should be at least 1 cm as a postfixation length of temporal artery less than 0.5 cm does increase the negativity rate, and many surgeons opt to remove 2 to 3 cm of artery.³³

Minor complications from this procedure include hematoma and wound infection. Facial nerve injury was reported by Murchison and Bilyk to be around 16% but was noted to resolve completely in over 50% of patients.³⁴ Damage to the branches of the facial nerve can lead to brow ptosis and/or orbicularis oculi weakness. This study noted that incisions less than 35 mm from the orbital rim and brow are at higher risk for this complication. Therefore, it is recommended that the incision be at least 35 mm from the orbital rim and above the brow.³⁴ The temporal branches of the facial nerve run deep to a loose alveolar layer of tissue. Therefore, care should be taken not to dissect deep to the STA fascia.^{35,36}

Histologically, GCA is characterized by the presence of inflammatory cells within the arterial wall, including lymphocytes, macrophages, and giant cells [see Figure 8, Figure 9, and Figure 10]. Multinucleated giant cells are seen on histology in only 50% of patients and are not necessary to establish the diagnosis of GCA. It is important to recognize that the vascular wall inflammation seen in the STA is often segmental and has characteristic “skip lesions.”³⁷

The incidence of false negative results of an STA biopsy may be affected by multiple factors, such as the length of the biopsy specimen, the presence of “skip lesions” that are frequently seen in GCA, pathologic sectioning, and the duration of steroid therapy prior to biopsy. It is often implied that patients with a negative biopsy will have their steroids discontinued. However, in at least one retrospective review, it was noted that frequently patients with a negative STA biopsy are continued on corticosteroids. The decision making in such cases is obviously more complex and relies on the clinical presentation, the physical examination, the evolution of the symptoms, and the response to medical therapy.³⁸

Table 4 Distribution of Arterial Lesions in GCA and TA*

Artery	GCA (%)	TA (%)
Left subclavian	61	69
Right subclavian	39	40
Left axillary	39	11
Right axillary	44	9
Mesenteric	18	36
Left renal	8	15
Right renal	16	16
Left carotid	21	37
Right carotid	17	25
Thoracic aorta	61	46
Abdominal aorta	42	37
Left iliofemoral	17	19
Right iliofemoral	13	20

GCA = giant cell arteritis; TA = Takayasu arteritis.

*Frequency of angiographic lesions in TA and GCA.²

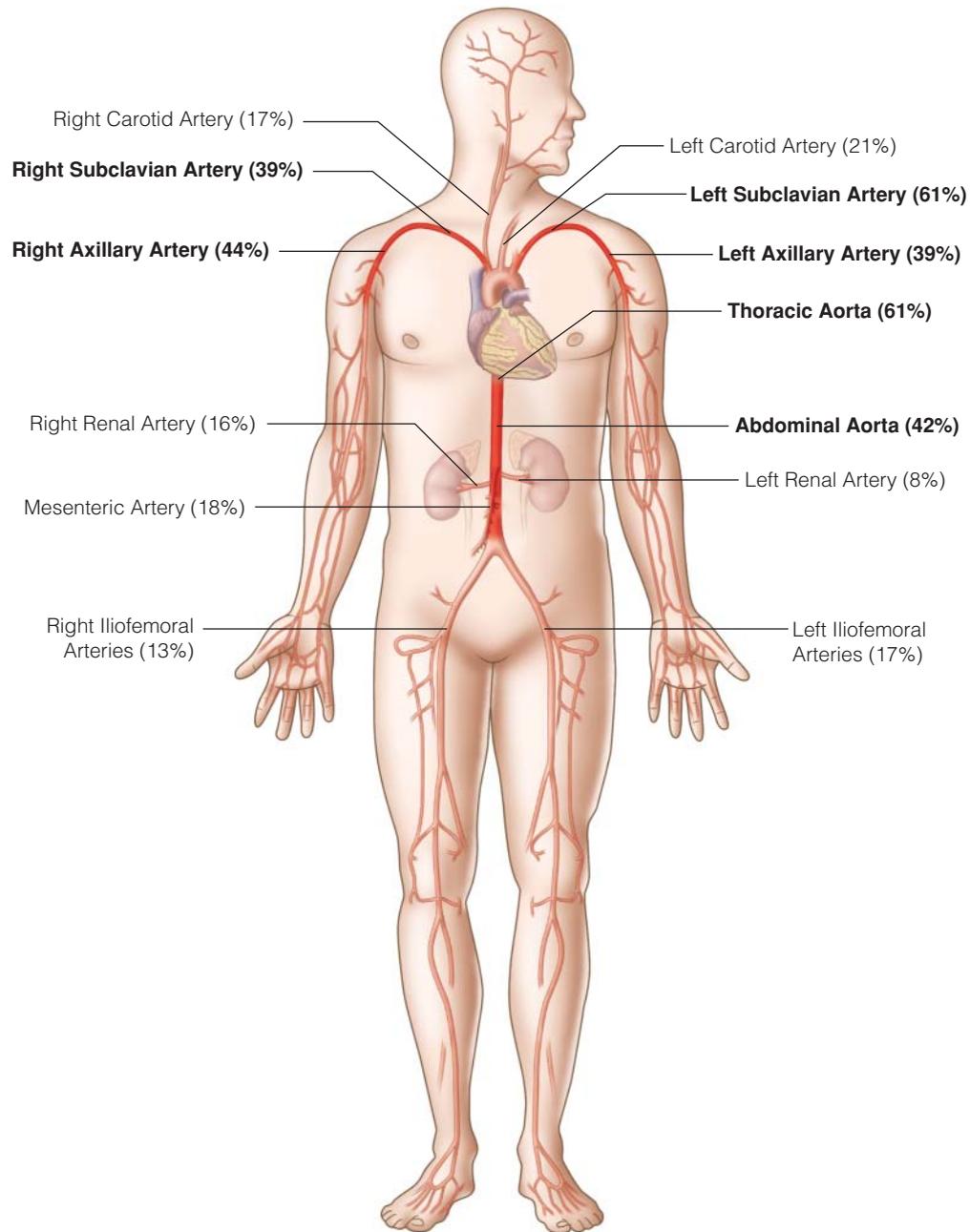
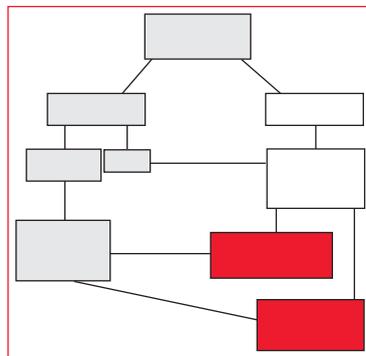


Figure 5 Frequency of arterial involvement in giant cell arteritis.²

TREATMENT

Medical Management

Glucocorticoids are the initial treatment of choice for patients with suspected GCA. The goal of steroid therapy is not only to suppress the inflammation but also to prevent further ischemic complications



of the disease. Unfortunately, if there has been visual loss prior to the initiation of steroid therapy, it is not reversible. The initial recommended dose of oral prednisone should be 40 to 60 mg per day.³⁹ There is some debate regarding whether intravenous methylprednisolone may be more beneficial than oral prednisone. When using methylprednisolone, doses of 15 mg/kg per day for 3 days in a pulsed manner may be used.⁴⁰ Treatment with corticosteroids should be continued for several weeks until the patient has clinically improved and the acute-phase reactants have normalized. At that time, a slow taper may be initiated. Most patients require at least a full year or more of steroid

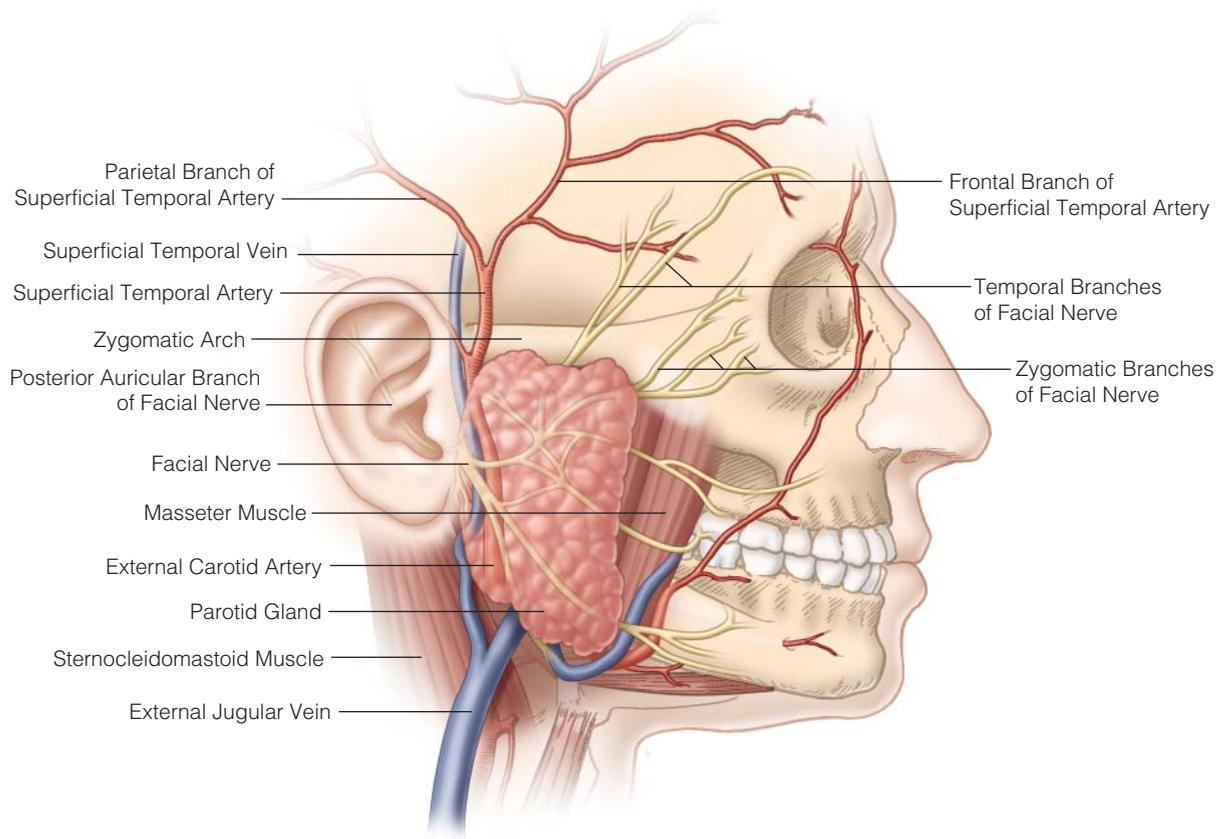


Figure 6 Anatomy of the superficial temporal artery and facial nerve. Note that the superficial temporal artery courses superiorly over the posterior aspect of the zygomatic arch. The facial nerve crosses the zygoma and travels anteriorly.

therapy. Clinical recurrences may occur in up to 50% of patients during the end of the steroid taper, with 30 to 50% of patients suffering from a relapse within the first 2 years.⁴¹

Methotrexate may be useful in a certain subgroup of patients with GCA, especially those who do not tolerate glucocorticoids. This medication may be beneficial, but the results of several randomized trials show conflicting results. A meta-analysis of these trials did suggest that there was a decreased risk of relapse with the use of methotrexate.⁴² Additionally, low-dose aspirin has been found to decrease the risk of ischemic complications.⁴³ It should be used cautiously in conjunction with corticosteroids and should always be combined with a proton pump inhibitor.

Surgical Management

Most patients demonstrate a marked improvement with medical management alone. However, there are patients who develop vascular complications, such as subclavian steal syndrome, chronic ischemia, aneurysmal degeneration, or aortic dissection. Caution should be advised when considering such patients with GCA for surgical intervention, especially in the acute inflammatory phase of disease.

Approximately 18 to 21% of patients with GCA will present with upper extremity arterial stenosis. Unlike chronic ischemia due to atherosclerotic disease, for which surgical revascularization is considered standard treatment, patients with GCA should be approached with caution. Fortunately,

such stenoses or occlusions often progress slowly, and there is time for a collateral network of vessels to develop and help compensate for the decreased blood flow. It is only when this collateral network is not sufficient that the patient will experience symptoms due to ischemia, such as claudication. In GCA, only 15 to 30% of patients develop chronic limb ischemia that will require some type of surgical or endovascular intervention.^{44,45}

If the patient has active GCA, bypass grafting should be avoided, if possible.⁴⁶ Bypass grafts performed in the presence of acute inflammation of the vessel wall, such as acute GCA, tend to have decreased patency. Generally, only in the case of aneurysmal degeneration, dissection, or subclavian steal syndrome should surgical intervention be considered and only after initiation of steroid therapy. Other types of chronic ischemia, such as chronic mesenteric ischemia due to GCA, generally respond well to medical management, and endovascular or surgical intervention should be avoided.⁴⁶

The subclavian arteries are frequently affected in GCA, with one study citing left subclavian artery involvement in 61% of patients and right subclavian artery involvement in 39%.² Therefore, subclavian steal syndrome is one such incidence when surgical intervention may be necessary in a patient with GCA. Subclavian steal syndrome occurs when the proximal subclavian artery is stenotic or occluded. Branches of the artery distal to the obstructed segment

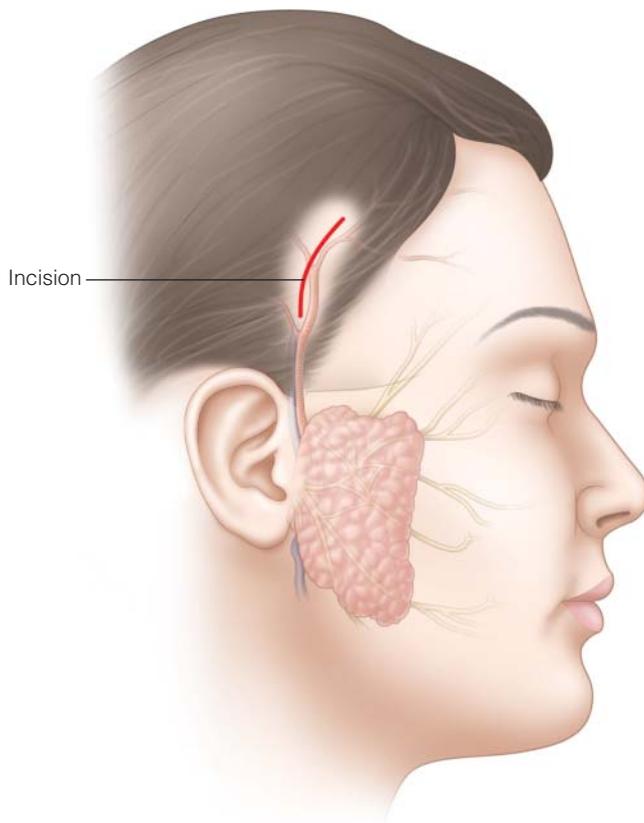


Figure 7 Placement of incision for superficial temporal artery biopsy. Note that shaving of the hairline is often required.

become collaterals to supply blood flow to the arm via flow reversal in the vertebral and/or internal mammary arteries. Carotid-subclavian artery bypass or an extra-anatomic bypass, such as a carotid-axillary or axilloaxillary bypass graft, are typical surgical procedures used for this purpose



Figure 8 Normal histology of the superficial temporal artery. Note that the lumen is widely patent. The intima, media, and adventitia are readily discernible.

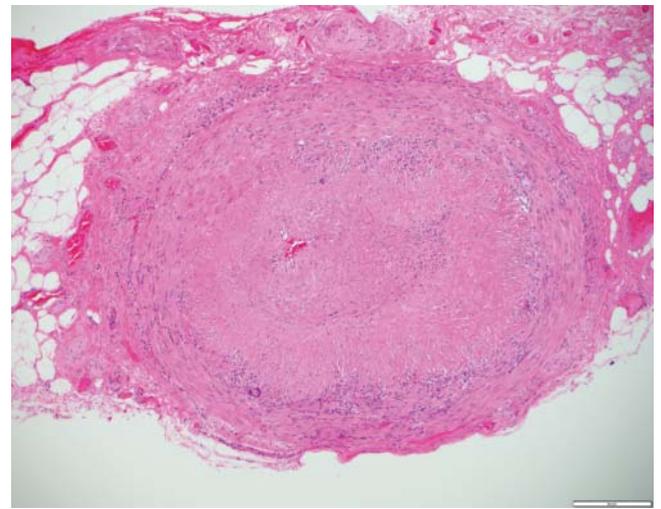


Figure 9 Histology of a superficial temporal artery in a patient with giant cell arteritis. Note that the lumen is occluded due to intimal hyperplasia. There is inflammation along the junction of the intima and media. There is a giant cell seen in the bottom left of the image.

in the nonacute phase of disease. Angioplasty and stenting of the proximally occluded subclavian artery are technically feasible, although restenosis appears to be quite common.⁴⁷⁻⁵¹

In addition to ischemic indications for surgical intervention, aneurysmal degeneration and aortic dissection may also develop due to GCA. When compared with the general population, patients with GCA are 17.3 times more likely to develop a thoracic aneurysm and 2.4 times more likely to develop an abdominal aortic aneurysm.⁵² It is important to note that aneurysms and dissections due to GCA may behave differently from aneurysms and dissections in the general population in terms of having a higher incidence of catastrophic complications and high mortality. In one study, 44% of patients died suddenly due to aortic dissection.⁵² In

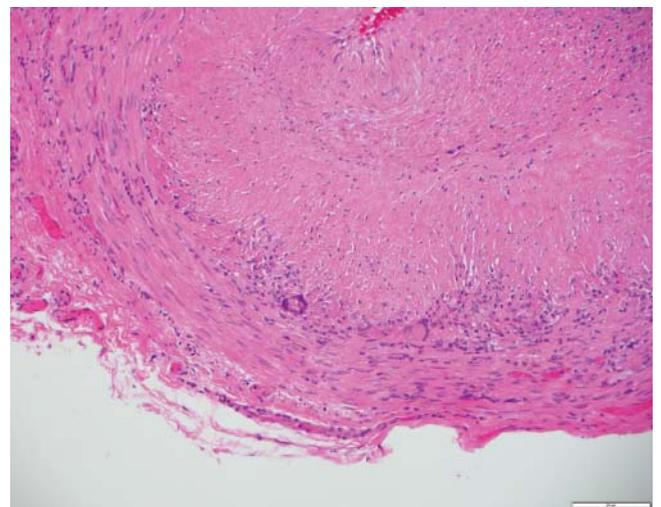


Figure 10 Higher magnification of the histology from a superficial temporal artery biopsy in a patient with giant cell arteritis. Note the giant cell at the bottom left of the image.

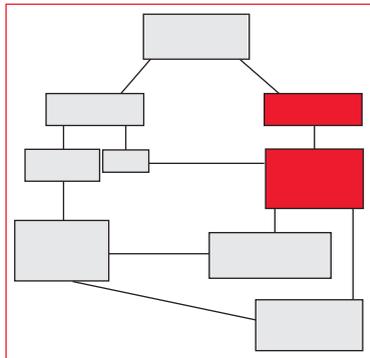
another series of 23 patients with aortic dissection, 46% of patients presented in acute distress and had an overall 2-week mortality of 80%, with fatal pericardial tamponade noted in 50% of these patients.⁵³ However, there are no large trials to confirm that the aneurysms in patients with GCA are more unstable than any other type of aneurysm. Therefore, most vascular surgeons use the same algorithm regarding indications for treatment for aneurysms due to atherosclerosis and aortic dissection due to nonvasculitic etiologies. However, it should be mentioned that early evaluation of the aorta and the great vessels for evidence of aneurysmal disease is warranted.

In terms of surgical treatment, both open and endovascular repair of aortic aneurysms and aortic dissection have been documented in the literature. Frequent surveillance of these patients following repair is required as new aortic pathology may present *de novo* following treatment. Patients may develop aneurysms elsewhere in the aorta or present with dissection distal to the region previously treated due to vessel fragility.^{54–56}

The ascending aorta may also demonstrate aneurysmal degeneration in up to 39% of cases.⁵⁷ Typically, this occurs from the aortic root through the aortic arch. It may present as aneurysm rupture or dissection with accompanying aortic regurgitation, stroke, or myocardial infarction.^{53,58,59} Additionally, aortic valve replacement may also be necessary, although the aortic valve tissue seems to be spared.⁵⁹ A study from the Mayo Clinic also demonstrated that nearly 50% of patients with ascending aortic aneurysms had other aneurysms of the thoracic and abdominal aorta and great vessels as well.⁶⁰ This finding again underscores that GCA affects the entire vascular tree and needs a comprehensive evaluation and close follow-up once diagnosed.

Takayasu Arteritis

TA, referred to as “pulseless disease,” is also a nonspecific granulomatous inflammatory arteritis of unknown etiology first described in 1908 by Mikito Takayasu, a Japanese ophthalmologist.⁶¹ Similarly to GCA, TA affects large vessels, especially the aorta and its major branches. Ultimately, the result of this arteritis may lead to either occlusive arterial disease and/or aneurysmal degeneration of the vessels involved in a manner similar to that seen in GCA.



EPIDEMIOLOGY

TA is typically diagnosed in patients under the age of 40 years, with most patients presenting in their teens or twenties. Most studies demonstrate a strong female predominance. Kerr and colleagues documented that 97% of TA patients were female in a study of 60 patients with TA arteritis over a 20-year period.⁶² Hall and colleagues documented an annual incidence of 2.6 cases per million in North America.⁶³ However, TA is most commonly seen in Asian

and Latin American countries.⁶⁴ There have been studies documenting that the incidence of occlusive versus aneurysmal disease varies based on geographic location. In Japan, the United States, and Europe, occlusive disease is more predominant, whereas aneurysmal disease is seen more commonly in India and Thailand.⁶⁵

ETIOLOGY

TA is a primary vasculitis, much like GCA, without an underlying etiology. However, associations have been noted with certain connective tissue disease, other autoimmune disorders, endocrine disorders, inflammatory bowel disease, and sarcoidosis.^{66,67}

DIAGNOSIS

In 1990, a classification system was developed by the American College of Rheumatology, in a manner similar to that for GCA. The purpose of this system was to highlight criteria present in TA to help distinguish it from other vasculitides [see Table 5].⁶⁸ There are six diagnostic criteria listed, including age at onset of disease less than or equal to 40 years, extremity claudication, diminished brachial artery pulse, difference in upper extremity systolic blood pressures of over 10 mm Hg, bruit over the subclavian arteries or aorta, and angiographic narrowing or occlusion of the entire aorta, its branches, or large arteries in the proximal upper or lower extremities. To make the diagnosis of TA, at least three of the six criteria must be met. In such cases, the sensitivity is 90.5% and the specificity is 97.8%.⁶⁸ It is important to note that this classification system is based on more advanced disease and is not as useful for patients in the beginning or prepulseless stage of TA.

CLINICAL MANIFESTATIONS: HISTORY AND PHYSICAL EXAMINATION

There are two distinct phases of TA, the initial acute inflammatory or systemic phase and the subsequent occlusive phase.⁶⁹ There may be some overlap between these two phases of disease, or they may occur months to years apart. Roughly 40 to 50% of patients present in the initial inflammatory phase. At this stage of disease, the patient will

Table 5 1990 Criteria for the Classification of Takayasu Arteritis*

1. Development of symptoms or findings related to Takayasu arteritis at age \leq 40 years
2. Development and worsening of fatigue and discomfort in muscles of one or more extremities while in use, especially the upper extremities
3. Decreased pulsation of one or both brachial arteries
4. Difference of $>$ 10 mm Hg in systolic blood pressure between arms
5. Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
6. Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental

*For purposes of classification, a patient shall be said to have Takayasu arteritis if at least three of these six criteria are present. The presence of any three or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%.⁶⁸

complain of nonspecific constitutional symptoms, such as fever, malaise, weight loss, and often tenderness over the affected arteries. Because these symptoms are nonspecific, often the diagnosis is not appropriately recognized. Fifty to 60% of patients will present in the second or “pulseless” phase of disease, where there is fixed occlusive or aneurysmal disease.

The patient’s symptoms in this “pulseless” phase will be directly related to the affected vessel and whether the patient has occlusive or aneurysmal changes in that vessel, similar to the presentation in GCA. Therefore, when taking a history from the patient, it is important to be comprehensive and include symptoms of claudication of the upper or lower extremities, hypertension (especially in children), neurologic symptoms, cardiac and pulmonary symptoms, and gastrointestinal and renal symptoms of ischemia. Over 50% of patients will develop neurologic manifestations, including headache, visual disturbances, cerebrovascular accident, or intracerebral hemorrhage [see Table 6].⁷⁰

With respect to the physical examination, a close examination of the vascular system from head to toe should be undertaken. Blood pressure should be checked in both arms, and any differential in systolic blood pressure should be noted. Hypertension, especially in children, may be a common finding, seen in approximately 50% of patients. All peripheral pulses in the upper and lower extremities should be palpated as Bicakcigil and colleagues documented that 88% of patients presented with absent or diminished pulses.⁷¹ Auscultation for bruits should be performed over the arterial beds. An ophthalmic examination is useful to examine for hypertensive retinopathy.

LABORATORY TESTS

There are no laboratory tests that are diagnostic for TA. The ESR may be high (over 50 mm/hr), especially during the initial inflammatory phase. However, the ESR is not specific and does not normalize over time, similar to GCA. Other laboratory abnormalities that may be noted include anemia, leukocytosis, hypergammaglobulinemia, and an increase in CRP.

Table 6 Clinical Presentation in TA Patients by Symptom*	
<i>Clinical Manifestation</i>	<i>%</i>
Systemic symptoms	66
Vascular symptoms	97
Absent or decreased pulses	88
Asymmetrical BP arms	81
Bruits	77
Hypertension	43
Ocular	36
CNS (stroke, TIA, visual changes)	63
Cardiac	57

BP = blood pressure; CNS = central nervous system; TA = Takayasu arteritis; TIA = transient ischemic stroke.

*Distribution of clinical signs and symptoms taken from study of 248 patients diagnosed with Takayasu arteritis in Turkey.⁶⁷

IMAGING

Conventional angiography, in conjunction with the clinical history and physical examination, has been the main diagnostic tool used to diagnose TA as a histologic diagnosis is not typically practical. However, conventional angiography is limited by the ability to evaluate only the arterial lumen, and it is unhelpful in distinguishing between active and inactive disease [see Figure 11]. For these reasons, CT or MR angiography and, to a lesser extent, ultrasonography are noninvasive tests that can help define the anatomic abnormalities associated with TA and offer some insight about the inflammatory reaction surrounding the vessels by evaluating for vessel wall thickening. For these reasons, CT angiography is often currently considered critical in the evaluation of the patient with suspected TA.⁷² FDG-PET has also shown some promise in terms of sensitivity and specificity for TA during the acute or inflammatory phase of the disease.^{73,74} It measures regional differences in glucose metabolism as inflammatory cells have an increased uptake of glucose. Thus, an increased uptake of FDG noted on a PET scan can be used to measure the degree of inflammation within the arterial wall during the inflammatory phase of the disease.⁷⁴ However, ultimately, the diagnosis is established through a combination of the overall clinical presentation in conjunction with the CT or MR angiographic findings.

The arteries most commonly involved, as per Grayson and colleagues, include the left and right subclavian arteries at 69% and 40%, respectively, the mesenteric arteries at 36%, the thoracic aorta at 46%, and the abdominal aorta at 37% [see Table 4 and Figure 12].² Less commonly seen lesions occur in the vertebral, axillary, brachial, and iliac arteries. Bilateral involvement is quite common.^{75,76} Again, the lesions

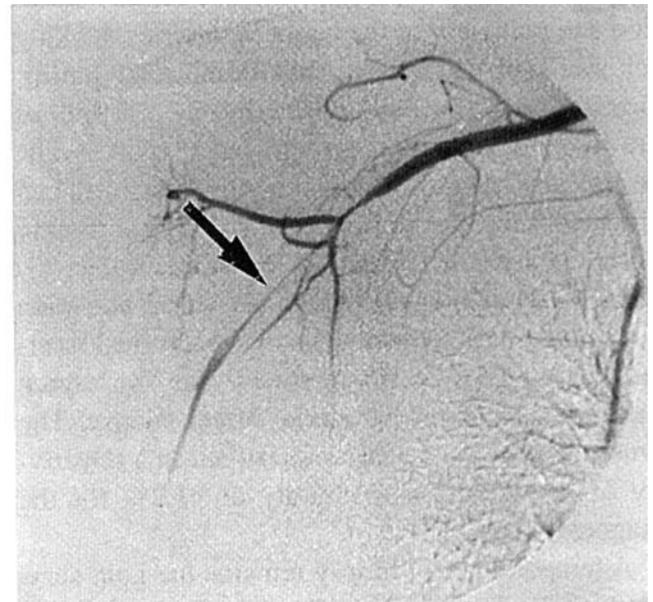


Figure 11 Conventional arteriogram of the right subclavian and axillary arteries in a patient with Takayasu arteritis. Note the long tapering stenosis of the axillary artery (arrow), which is characteristic of Takayasu arteritis.

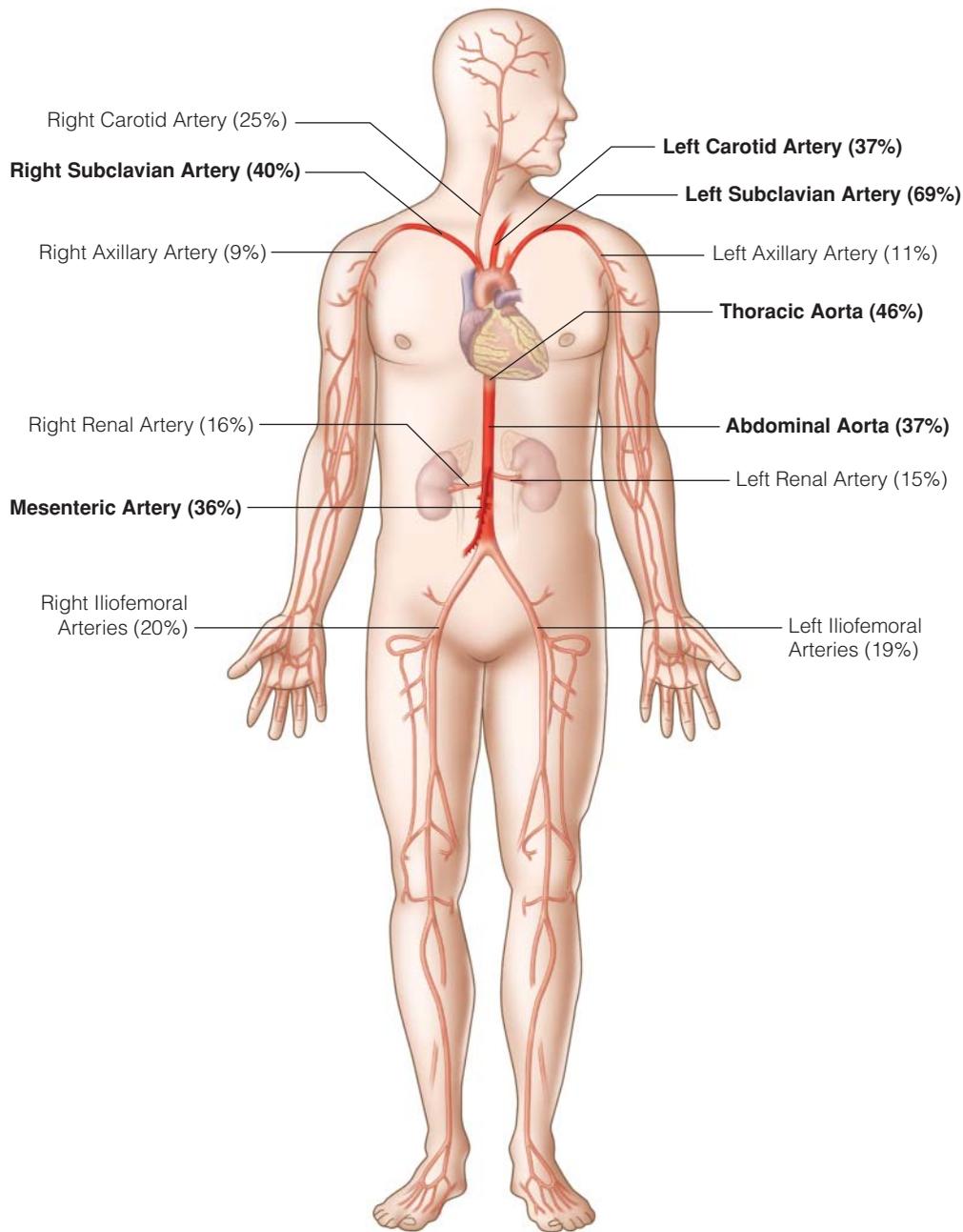


Figure 12 Frequency of arterial involvement in Takayasu arteritis.²

found with respect to these arteries will be regions of stenosis or occlusion or aneurysmal degeneration. The clinical picture depends on the vessel affected as to whether the patient presents with limb claudication, bruits, pulse deficits, hypertension, or aneurysms.

TREATMENT

Medical Management

Corticosteroid administration is the first-line medical therapy in the treatment of TA and should be initiated as soon as the diagnosis of TA is suspected.⁷⁷ The typical

regimen includes prednisone at 1 mg/kg/day doses for 1 month followed by a slow taper leading to eventual discontinuation of the drug.⁷⁷ Unfortunately, relapses do occur, and 66 to 84% of patients require additional immunosuppressive agents.⁷⁸ Methotrexate, azathioprine, and mycophenolate mofetil may be used for relapsing disease.^{79–81} One study documented that patients who received low-dose aspirin had a lower incidence of ischemic events.⁸²

Surgical Treatment

Although many patients respond to medical therapy, there is a subset of patients who develop complications from

the arteritis necessitating surgical intervention, usually for either occlusive or aneurysmal disease. The literature suggests that less than 20% of patients with TA will ultimately require surgery.^{83,84} Ideally, surgical intervention in TA should be performed during a period of quiescence and in the absence of elevated inflammatory markers. It has been well documented that the rate of failure is around sevenfold greater when procedures are performed in patients with acute inflammation.⁸⁵ Should surgical intervention be necessary during the acute inflammatory phase, every effort should be attempted to situate the distal anastomosis to arterial segments that are free of inflammation. Additionally, steroid therapy should be initiated prior to surgery.

As TA may manifest itself in a number of arterial beds, the initial symptomatic manifestations may include renovascular hypertension, upper or lower arterial ischemia, aortic insufficiency, aneurysmal disease, or cerebrovascular issues. As a result, the surgical procedures required for a patient with TA may be quite varied.

For patients who present with renovascular hypertension, aortorenal bypass is typically considered the gold standard if possible. Occasionally, nephrectomy is required.⁸⁶ There have been reports of successful transluminal renal angioplasty. However, stent placement should only be selectively used in these patients.^{86,87}

Arm ischemia typically involves stenosis or occlusion of the subclavian arteries. Carotid to subclavian, axillary, or brachial artery bypass grafting is often necessary to bypass the affected segment of subclavian artery. Similar principles are applied to lower extremity ischemia. When the distal juxtarenal or infrarenal aorta is affected, bypass around this region typically requires proximal aortic to iliac or femoral bypass grafting. Finally, for cerebrovascular occlusive disease, aortic to subclavian or carotid bypass grafting may be necessary.⁸⁶ Patch angioplasty and/or endarterectomy should be avoided due to disappointing results in TA patients with inflamed arteries.^{88,89}

Conclusions

GCA and TA are the two most common of the large vessel vasculitides. They may have distinctly different clinical presentations, in terms of patient age and sex and in how the diagnosis is ultimately confirmed. However, there are distinct similarities between these two diseases. In fact, there are so many similarities that it is commonly believed that they should be viewed as a continuum within one disease state. As surgeons, it is critically important that we are able to distinguish between patients who should be managed medically and those who need urgent operation. Most patients with chronic ischemia can and should be treated with medical management initially, during which many improve significantly. Very few patients necessitate surgical or interventional procedures, but these surgical procedures are best performed while the patient is on steroids and following the acute inflammatory phase of the disease.

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